Comparative study of different treatment options of grade III and IV diabetic foot ulcers to reduce the incidence of amputations

Sachin Khandelwal, Poras Chaudhary, Dev Datta Poddar, Neeraj Saxena, Rana A.K. Singh, Upendra C. Biswal

Dr Ram Manohar Lohia Hospital and PGIMER, New Delhi, India

Abstract

This study aims to compare the efficacy of antiseptic dressings, hyperbaric oxygen therapy, and recombinant human platelet derived growth factor (rhPDGF) for two reasons: i) to reduce the incidence of lower limb amputations in diabetic foot ulcer; ii) to limit the duration of stay in the hospital. A prospective randomized trial was conducted on 60 patients with stage III and IV diabetic foot ulcers (International Association of Enterostomal Therapy classification) and patients were divided randomly in three different therapy groups - antiseptics, hyperbaric oxygen therapy, recombinant platelet derived growth factor, with 20 patients in each group. Patients were managed initially on inpatient and then on outpatient basis till the ulcer healed completely. Results among three groups were compared using unpaired T test and the level of significance was set at P<0.05 using ANOVA. This study compares the efficacy of hyperbaric oxygen therapy, antiseptic dressings, and rhPDGF in grade III and IV diabetic foot ulcers. P value (0.0348) was significant for complete wound contraction while p value healing time (0.6534) and ulcer size (0.0593) in the groups was not significant. PDGF is safe, effective and easy to apply. Results are comparable with hyperbaric oxygen (HBO) therapy and cost of treatment is lower than other therapies. Diabetic foot ulcer management requires multidisciplinary and aggressive approach. PDGF should be recommended for all grade III and IV diabetic foot ulcer at least 8 weeks old. HBO is equally good an option but has limitations and side effects.

Introduction

Diabetes mellitus is characterized by a state of hyperglycemia, resulting from a diversity of etiologies, environmental and genetic, acting jointly [World Health Organization's definition (WHO, 1980)]. Chronic hyperglycemia, from whatever cause, leads to a number of complications- cardiovascular, renal, neurological, ocular and recurrent infections. The WHO defines diabetic foot as the lower limb of a diabetic patient that has the potential risk of pathologic consequences, including infection, ulceration, and/or destruction of deep tissues associated with neurological abnormalities, various degrees of peripheral vascular disease, and/or metabolic complications of diabetes.

The risk of lower extremity amputation is 15 to 46 times higher in diabetics[1] and lower limb amputations are associated with diabetes in 40% to 90% of cases. Among diabetics, about 15% may experience a foot ulcer in their lifetime and about 14-24% of them may require an amputation.[2] In India the prevalence of foot ulcer is 2.1% to 12.4% among diabetics. Early detection and appropriate treatment of these ulcers may prevent large number of these amputations. Clinical studies show that foot ulcers precede 85% of non traumatic lower extremity amputations among diabetics.[3] The factors related to the development of foot ulcers are peripheral neuropathy, minor foot trauma, and foot deformities.[4] Percentages of 60% to 70% of diabetic foot ulcers are purely due to peripheral neuropathy, 15% to 20% to peripheral vascular disease, and the remaining are related to a combination (neuroischemia). The annual population based incidence of foot ulcers in people with type 1 or 2 diabetes is 1.9% to 2.2%.[5-7] This study is an attempt to compare three treatment options *viz.* simple dressing, hyperbaric oxygen therapy and platelet derived growth factor gel, in patients with stage 3 and 4 diabetic foot ulcer [International Association of Enterostomal Therapy (IAET) classification], and their role in reducing the incidence of amputation. We have utilized IAET[8] classification (Table 1) for staging of diabetic foot ulcers in our study as this classification is preferable for evaluation because most of studies have utilized this classification for evaluation of the treatment because of its ease and simplicity.[9,10] An ideal classification system should be easy to use, practical and clear. It should be based more on objective criterion and measurements while minimizing subjective variations. Other classifications for diabetic foot ulcers are given in Tables 2-4.

In this study we have compared platelet derived growth factor (PDGF) gel with antiseptic dressings and hyperbaric oxygen therapy. PDGF consists of a family of growth factors consisting of two polypeptide chains (A and B) which forms the dimers, or protein pairs: PDGF (AA, AB, BB). Recombinant human (rh)PDGF-BB is the only topical growth factor to be approved for the purpose of wound healing. It belongs to selected group of products that claim to improve wound healing by increasing the incidence of wound closure. Published literature shows that daily application of rhPDGF has only negligible systemic absorption.[11]

PDGF mediates tissue repair via:[12] i) mitosis of mesenchymal cells including dermal fibroblasts, smooth muscle cells and wound capillary endothelial cells (angiogenesis); ii) chemoattraction of fibroblasts, smooth muscle cells, monocytes and neutrophils; iii) induction of extracellular matrix components in fibroblasts, including fibronectin and hyaluronic acid; iv) induction of metalloproteinases involved in wound remodeling.

Hyperbaric oxygen (HBO) therapy is defined as intermittent administration of 100% oxygen inhaled at pressure greater than sea level. The technique may be implemented in a walk-in multiplace chamber compressed to depth with air while the person breathes 100% oxygen via head tent, face mask, or endotracheal tube. Multiplace chambers accommodate up to six patients at a time; each patient is given an individual breathing source.[13] Alternatively the patient may be treated in one person monoplace chamber pressurized to depth with oxygen. In either case, the arterial pressure of oxygen will approach 1500 mm Hg at the pressure equiva-

Correspondence: Poras Chaudhary, Lady Hardinge Medical College and associated Dr Ram Manohar Lohia Hospital, 189, Deoli Road, Khanpur New Delhi 110062, India.
Tel. +91.9891.4473.358.
E-mail: drporaschaudhary@yahoo.com

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lent of 2 atmospheres absolute. Hyperbaric oxygen given in this manner, also referred to as systemic hyperbaric therapy should not be confused with topical oxygen therapy (in limb encasing devices) or pure oxygen inhaled at ambient atmospheric pressure.

Materials and Methods

Study design

This was a single centre study comparing the effect of three different treatment options - antiseptic dressing, hyperbaric oxygen therapy, and platelet derived growth factor on stage III and IV diabetic foot ulcer. It was performed between December 2007 and march 2009. Following the screening visit and confirmation of eligibility, 60 patients were randomized to one of the three treatment groups in 1:1:1 ratio for management of diabetic foot ulcers. The protocol was approved by Dr Ram Manohar Lohia (RML) Hospital (New Delhi, India) and Postgraduate Institute of Medical Education & Research (PGIMER) Ethical Review Board (New Delhi, India). According to the principles of the declaration of Helsinki 1975, written , informed consent was obtained from all participants.

Participants

All patients presented in Dr RML Hospital outpatient department and emergency were assessed. Seventy-five patients were enrolled, 15 excluded. Participants were aged between 35 and 65 years, they had type 2 diabetes mellitus and was adequately controlled. Inclusion criteria were: diabetic foot ulcer of at least 8 weeks duration, patients with only Stage III and IV diabetic foot ulcer, absence of vascular insufficiency involving large and medium sized arteries proximal to the ulcer demonstrated by Doppler study, age ≥18 years with type 1 or 2 diabetes. Exclusion criteria were: patients with uncontrolled diabetes, foot ulcer with established gangrene, compromised vascularity of the particular limb, associated osteomyelitis at site of ulcer, pregnant and lactating females, neoplasm at the local site, patients on any immunosuppressive agents, presence of multiple ulcers, patients who were HIV seropositive, with known drug allergy, presence of concomitant life threatening infections, chronic renal insufficiency (serum creatinine >3 mg/dL), when ear cannot equalize the pressure when congested with cold/hay fever, patients with perforation of ear drum. High risk case *i.e.* bronchial asthma/emphysema.

Diagnostic criteria for diagnosis of diabetes mellitus

Diagnostic criteria for diagnosis of diabetes mellitus are: i) symptoms of diabetes plus casual plasma glucose level more than 200 mg/dL (11.1 mmol/L). Casual is defined as any time of the day without regard to time since last meal. The classic symptoms of diabetes includes polyuria/polydipsia and unexplained weight loss; ii) fasting glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h; iii) 2 h blood glucose ≥200 mg/dL during an oral glucose tolerance test (OGTT). OGTT: the test should be as described by WHO, using a glucose load containing the equivalent of 75 mg anhydrous glucose dissolved in water.

Patients were randomly divided into three different treatment groups - I, II, and III. Group 1 patients were treated with antiseptics, group 2 with HBO therapy, and group 3 with rhPDGF-BB. Patients were treated either in wards or on outpatient basis.

In addition to all the routine investigations including fasting blood sugar, pretreatment X-ray of the limb was done to rule out osteomyelitis. Doppler study of the particular limb was performed to rule out vascular compromise. Antibiotics were started depending upon pus culture reports.

Each patient was a part of the study for 10 weeks or till the ulcer healed, during which efficacy of that particular treatment was evaluated by wound contraction rate which was calculated by the formula, greatest length x greatest breath of the ulcer (post debridement) in cm^2, before and after treatment.

Table 1. International Association of Enterostomal Therapy classification.

Stage I	Non-blanchable erythema of intact skin; the heralding lesion of skin ulceration.
Stage II	Partial thickness skin loss involving epidermis and/or dermis. Ulcer is superficial and presents clinically as an abrasion, blister, or shallow crater.
Stage III	Full thickness skin loss involving damage or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia. The ulcer presents clinically as a deep crater with or without undermining of adjacent tissue.
Stage IV	Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone, or supporting structures (*viz.* tendon or joint capsule).

Table 2. Wagner-Meggitt classification.

Grade 0	Preulcerative lesion.
Grade 1	Partial thickness wound up to but not through the dermis.
Grade 2	Full thickness wounds extending to tendons or deeper subcutaneous tissues but without bony involvement or osteomyelitis.
Grade 3	Full thickness wound extending to and involving bone.
Grade 4	Localized gangrene.
Grade 5	Gangrene of whole foot.

Table 3. Depth-Ischemia classification.

Depth classification	
0	At risk foot; previous ulcer or neuropathy with deformity that may cause new ulceration.
1	Superficial ulceration not infected.
2	Deep ulceration exposing a tendon or joint (with or without superficial infection).
3	Extensive ulceration with exposed bone/and or deep infection (i.e. osteomyelitis or abscess).
Ischemia classification	
A	Not ischemic.
B	Ischemia without gangrene.
C	Partial (forefoot) gangrene of foot.
D	Complete foot gangrene.

Table 4. University of Texas wound classification.

	Grade 0	Grade I	Grade II	Grade III
Stage A	Preulcerative or postulcerative lesions completely epithelialized	Superficial wound, not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
Stage B	Infection	Infection	Infection	Infection
Stage C	Ischemia	Ischemia	Ischemia	Ischemia
Stage D	Infection and ischemia	Infection and ischemia	Infection and ischemia	Infection and ischemia

Group 3: platelet derived growth factor therapy

The patients in this group were initially derided surgically and subsequently as well as and when required. The ulcer was treated with daily local application of commercially available PDGF gel. The patients were initially followed daily by asking them to visit the hospital daily. As the ulcer got better with time, or the patient and attendants learnt the correct method of application; the visits were reduced. The dose of the gel was revised at regular intervals.The intended dose for topical application is around 7 μg/cm² of ulcer per day for a person with average weight of 50 kg. The amount of gel to be applied also varies depending upon the size of the ulcer. The approximate length of gel to be squeezed out from the tube=greatest length of the ulcer x greatest width of the ulcer in inches or centimeters multiplied or divided respectively by and factor as given in the Table 5.

Table 5. Factor to calculate dose for topical application.

Unit of measurement	Factor	Amount of gel per unit length of tube squeezed
Inch	Multiply by 0.6	0.65 gm (65 μg)
Centimeter	Divide by 4	0.25 m (25 μg)

Table 6. Analysis of results.

Variables	Group I	Group II	Group III
No.	20	20	20
Mean age (years)	45=7.574	43.8=9.4	43.35=8.1
SEM	1.694	2.1	1.8
Gender	Male=11	Male=10	Male=11
Mean ulcer healing time (weeks)	6.75=2.65	6.83=2.5	7.6=2.53
% of ulcers showing complete healing	40	60	80
Mean ulcer size group	9.90=5.593 cm²	14.91=6.23 cm²	19.26=11.315 cm²
No. of patients lost to follow up	6 (30%)	5 (25%)	1 (5%)

SEM, standard error mean.

Method of application

After dose calculation, gel was applied once in 24 h. Hands were washed thoroughly before applying gel. Before each application, the ulcer was gently rinsed with saline or water to remove any residual gel and wound area cleaned or debrided, if needed. The gel was then covered with saline moistened gauze and a secondary dressing and left for approximately 24 h. After 24 h the gel was gently rinsed off using saline or water and reapplied.

Group 2: hyperbaric oxygen therapy

Patients in this group were taken for HBO therapy at 2.5 ATA for 60 min per sitting for a total of 30 sittings or till the ulcer healed. These sittings were distributed over a period of 10 weeks. Patients were given either daily or alternate day therapy depending on the availability of slot in the facility. The patients in this group were also debrided from time to time but dressed only with normal saline. No antiseptics were used.

Method of administration

The standard protocol of HBO therapy is followed as per the guidelines under supervision of an anesthetist and expert technical staff.

Single patient is placed in a monoplace chamber, which is pressurized with 100% oxygen. The treatment control panel controls the therapy and monitors the patients during the treatment. Surgical dressings were not removed for treatment to be administered. Patients were not allowed to smoke during the entire course of HBO therapy. The efficacy of this treatment was measured by the % of ulcers with complete healing at the end of the treatment schedule.

Group 1: antiseptic dressings

Patients belonging to Group 1 were surgically debrided at their initial visit and then treated with following agents:

- EUSOL: Patient's foot was immersed in freshly prepared EUSOL solution for half an hour. Fresh preparation of this solution in standard concentrations was made daily in the wards.
- For the patients who were treated on outpatient basis commercially available EUSOL was used.
- Following treatment with EUSOL, hydrogen peroxide (H_2O_2) was used on the patient's foot followed by povidone iodine. The ulcer was then dressed with saline gauze followed by secondary dressing.
- Dressing was opened after 24 h and it was repeated.

In this group as well efficacy was measured by % of ulcers with complete healing at the end of the treatment schedule.

Statistical analysis

The results were evaluated using unpaired T test. The level of significance was set at $P<0.05$ using ANOVA.

Results

Different variables given in Table 6 were analyzed.

General characteristics

Of 20 patients in Group I, 11 were males (55%), with mean age of 45=7.57 years. In Group II, ratio of male to female was equal with mean age of 43.8=9.4 years. In Group III, 11 patients were males (55%), with a mean age of 43.25=8.1 years.

Number of patients lost to follow up were 6 (30%) in Group I, 5 (25%) in Group II, and 1

(5%) in Group III.

- *Comparing healing time of three groups:* P value using ANOVA=0.6534 , not significant.
- *Comparing individual groups using UNPAIRED T-Test:* i) Groups III and II: P value 0.4374, not significant; ii) Groups III and I: P value 0.4558, not significant; iii) Groups II and I: P value 0.9433, not significant. Individual P values are the two tailed P values.
- *Comparing % of patients with complete healing, in three groups:* P value using ANOVA=0.0348, considered significant. Variation among column means is significantly greater than expected by chance.
- *Comparing ulcer size:* P value using ANOVA=0.0593, not quite significant.
- *Comparing individual groups using UNPAIRED T-Test:* i) Groups III and I: P value 0.0393, significant; ii) Groups III and II: P value 0.2415, not significant; iii) Groups II and I: P value 0.0835, not significant (Figures 1-3).

Discussion

Surgical management of diabetic foot ulcers continues to receive considerable attention in view of its debilitating complications. Previously various trials have been done regarding role of HBO therapy and rhPDGF in diabetic foot ulcers. This randomized prospective trial compares the efficacy of HBO, rhPDGF and antiseptic dressings in Grade III and IV diabetic foot ulcers (IAET classification), in 60 Indian patients.

In the present study P value for healing time is 0.6534 which is not significant. Even the individual P values were not significant. Various international and Indian trials have firmly established better healing time with HBO and rhPDGF compared to conventional dressings. A significant reason for this kind of a result could have been the small sample size of this study. To be a part of the Gaussian population, the sample size has to be adequate. What should be the adequate sample size could not be commented upon but previous international studies have been done with 382[14] and 925[15] patients respectively. A bigger study group would have given a better understanding on this issue.

As we compared the groups using % of patients with complete wound contraction, P value comes out to be 0.0348, which is significant. Complete healing % of rhPDGF (80%) was significantly higher than HBO therapy (60%) which is again significantly higher than those of antiseptic dressings (40%). In all the groups, on comparing ulcer size, the P value was found to be 0.0593, which is not significant (>0.05). All the same, we would call it not

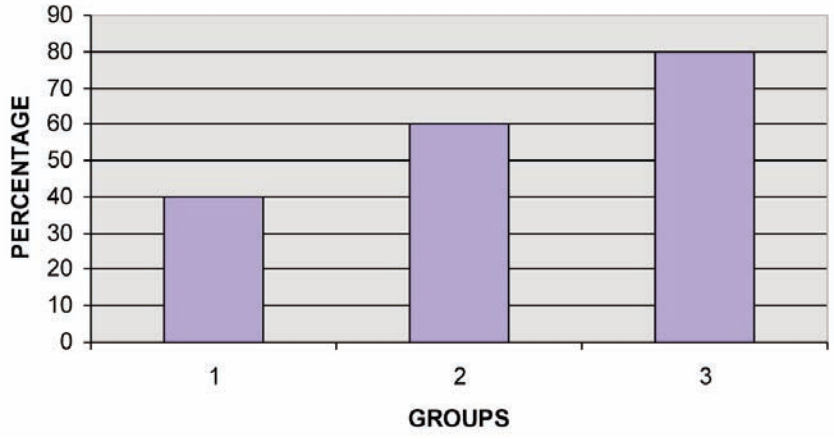

Figure 1. Patients (%) with complete healing.

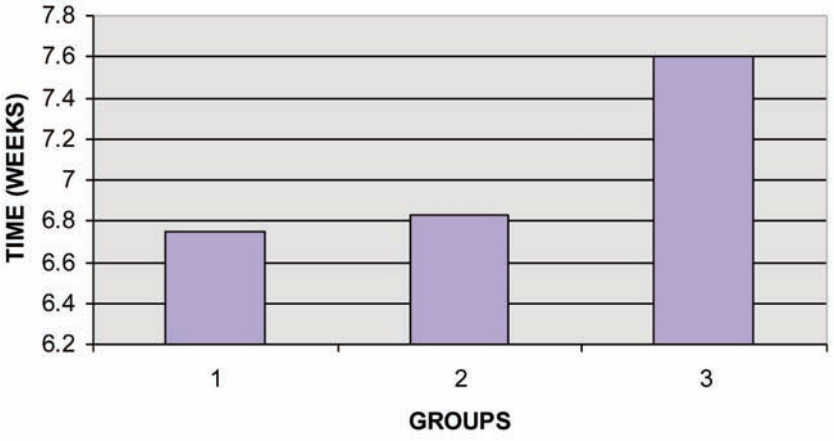

Figure 2. Mean ulcer healing time (weeks).

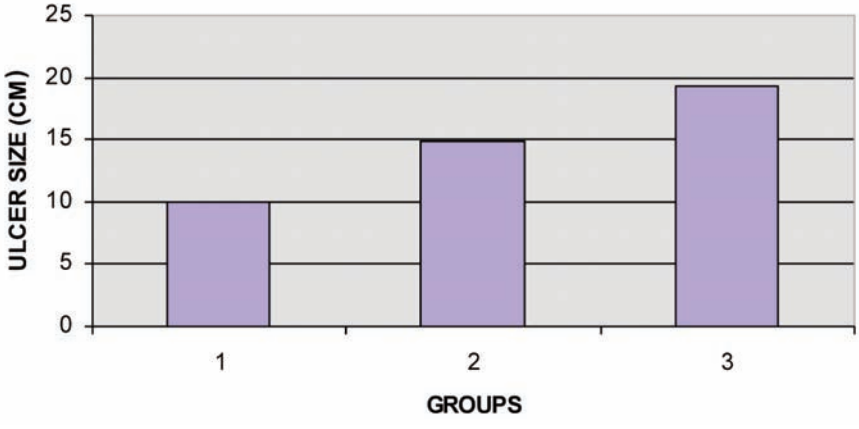

Figure 3. Mean ulcer size (cm).

that significant because it is very close to 0.05. Again a greater size of the study group would have given a clearer picture. In this on comparing rhPDGF with antiseptic dressings p value came out to be 0.0393 which is actually significant and this could possibly one of the reasons for longer healing time in PDGF group.

One unique feature of this study was the comparison made between HBO therapy and PDGF. Healing time was not significant but % of patients with complete wound contraction was significantly higher in the PDGF group, which was our primary efficacy criteria. Moreover if we see the actual no of patients leaving the study was higher in HBO group as compared to PDGF. In a country like India where socioeconomic issues play a major role asking them to come daily to hospital for HBO therapy is not always feasible. PDGF can be safely and effectively applied at home. Apart from that side effects seen with HBO therapy like claustrophobia, ear ache, near sightedness, dry cough are not a problem with PDGF (this study has not commented upon the actual no of patients developing these side effects). All the absolute and relative contraindications of HBO therapy are not a problem with PDGF. Cost of treatment is lower with PDGF as compared to HBO therapy and HBO therapy requires and big setup which is only possible with tertiary care hospitals which is not and problem with PDGF which can even be given in primary care settings. So PDGF is equally good an option in diabetic foot patients with added advantages as mentioned above. The current treatment protocol recommends use of growth factor if the wound is not healing after 8 weeks of employing traditional therapy modalities.[16]

Regarding dressings with antiseptics like betadine, H_2O_2 and EUSOL, although mean ulcer healing time is not significantly different among three groups, an international consensus has built up regarding their harmful effects on tissue architecture and they are no longer recommended. Antiseptic agents such as hydrogen peroxide and chlorhexidine are safe for intact skin but toxic to human fibroblasts and other cell types, so are no longer used for diabetic foot wounds.[17] Iodide-based agents are toxic and should not be used.[14] In a country like India economic losses to the patients in terms of daily wages should also be considered which would be low with PDGF group as shown in other studies because of low healing time with growth factors (although this study does not exactly compare man hours lost among three groups). Moreover they do not have any added advantage over PDGF and HBO therapy (lower complete wound contraction rate). But in India antiseptic agents are still being used at many institutions either because of individual financial constraints or lack of medical expertise. This study does not aim to refute antiseptics altogether and gives due respect to individual clinical experience of doctors treating diabetic foots. A larger multi-institutional study would be required to comment on the above issue.

Conclusions

Diabetic foot ulcer management requires multidisciplinary and aggressive approach.

PDGF should be recommended for all grade III and IV diabetic foot ulcer at least 8 weeks old. HBO is equally good an option but has all the limitations and side effects as mentioned. Further studies needs to be done to prove the superiority of PDGF over HBO or *vice versa*. Antiseptic agents should be avoided if possible used for treating diabetic foot ulcers.

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